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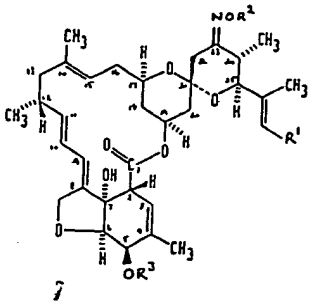
(54) Macrolide compounds

(57) Compounds of formula (I)



(I)

and salts thereof, wherein

R^1 represents a methyl, ethyl or isopropyl group;

R^2 represents a hydrogen atom, a C_{1-8} alkyl group or a C_{3-8} alkenyl group and the group $=NOR^2$ is in the E-configuration;

OR^3 is a hydroxyl group or a substituted hydroxyl group having up to 25 carbon atoms, may be used for *controlling insect, acarine, nematode* or *other pests.*

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SPECIFICATION

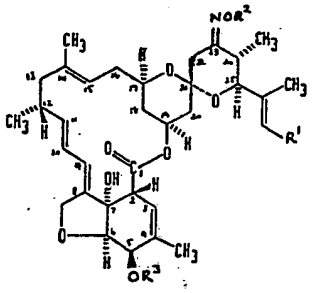
Macrolide compounds

This invention relates to novel antibiotic compounds, to processes for their preparation and to pharmaceutical compositions containing them.

In our United Kingdom Patent Specification 2166436 we describe the production of Antibiotics S541 which may be isolated from the fermentation products of a novel *Streptomyces* sp.

We have now found a further group of compounds with antibiotic activity which may be prepared by chemical modification of Antibiotics S541.

Thus, in one aspect, the invention particularly provides the compounds of formula (1)



(I)

and salts thereof, wherein R^1 represents a methyl, ethyl or isopropyl group; R^2 represents a hydrogen atom, a C_{1-8} alkyl group or a C_{3-8} alkenyl group; OR^3 is a hydroxyl group or a substituted hydroxyl group having up to 25 carbon atoms; and the group $=NOR^2$ is in the E configuration.

The term 'alkyl' or 'alkenyl' as a group or part of a group in the compounds of formula (I) means that the group is straight or branched.

When R^2 in the compounds of formula (I) ia a C_{1-8} alkyl group, it may be for example a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl or t-butyl group, and is preferably a methyl group.

When R^2 is a C_{3-8} alkenyl group, it may be for example an allyl group.

When the group OR^3 in compounds of formula (I) is a substituted hydroxyl group it may represent an acyloxy group [e.g. a group of the formula $-OCOR^4$, $-OCO_2R^4$ or $-OCSOR^4$ (where R^4 is an aliphatic, araliphatic or aromatic group, for example an alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl or aryl group)], a formyloxy group, a group $-OR^5$ (where R^5 is as defined above for R^4), a group $-OSO_2R^6$ (where R^6 is a C_{1-4} alkyl or C_{6-10} aryl group), a cyclic or acyclic acetaloxy group, a group $OCO(CH_2)_nCO_2R^7$ (where R^7 is a hydrogen atom or a group as defined for R^4 above and n represents zero, 1 or 2) or a group $OCONR^8R^9$ (where R^8 and R^9 may each independently represent a hydrogen atom or a C_{1-4} alkyl group e.g. methyl).

Where R^4 or R^5 are alkyl groups, they may be for example C_{1-8} alkyl groups e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl or n-heptyl which alkyl groups may also be substituted. Where R^4 is a substituted alkyl group it may be substituted by, for example, one or more, e.g. two or three halogen atoms (e.g. chlorine or bromine atoms), or a carboxy, C_{1-4} alkoxy (e.g. methoxy, ethoxy), phenoxy or silyloxy group. Where R^5 is a substituted alkyl group it may be substituted by a cycloalkyl e.g. cyclopropyl group.

Where R^4 or R^5 are alkenyl or alkynyl groups, they may be for example C_{2-8} alkenyl, e.g. allyl, or C_{2-8} alkynyl groups.

Where R^4 or R^5 are cycloalkyl groups, they may be for example C_{3-12} cycloalkyl, such as C_{3-7} cycloalkyl, e.g. cyclopentyl groups.

Where R^4 or R^5 are aralkyl groups, they preferably have 1 to 6 carbon atoms in the alkyl moiety and the aryl group(s) may be carbocyclic or heterocyclic and preferably contain 4-15 carbon atoms e.g. phenyl. Examples of such groups include phenC_{1-6}alkyl, e.g. benzyl groups.

Where R^4 or R^5 are aryl groups, they may be carbocyclic or heterocyclic and preferably have 4-15 carbon atoms, and may be for example a phenyl group.

When R^4 contains a silyloxy substituent, the silyl group may carry three groups which may be the same or different, selected from alkyl, alkenyl, alkoxy, cycloalkyl, aralkyl, aryl and aryloxy groups. such groups may be as defined above for R^4 and particularly include methyl, t-butyl and phenyl groups. Particular examples of such silyloxy groups are trimethylsilyloxy and t-butyldimethylsilyloxy.

When $-OR^3$ is a group $-OSO_2R^6$, it may be for example a methylsulphonyloxy or p-toluenesulphonyloxy group.

Where $-OR^3$ represents a cyclic acetaloxy group, it may for example have 5-7 ring members and may be for example a tetrahydropyranyloxy group.

Wher OR^3 r pres nts a group $OCO(CH_2)_nCO_2R^7$, it may for xample be a group $OCOCO_2R^{7a}$ or $OCOCH_2CH_2CO_2R^{7a}$ where R^{7a} represents a hydrogen atom or a C_{1-4} alkyl (e.g. methyl or ethyl) group.

Salts that may be formed with compounds of formula (I) containing an acidic group include salts with bases e.g. alkali metal salts such as sodium and potassium salts.

In the compounds of formula (I), the group R^1 is preferably an isopropyl group.

The group OR^3 is preferably a methoxycarbonyloxy, or, especially, an acetoxy, methoxy or hydroxy group. In general, compounds of formula (I) in which OR^3 is a hydroxy group are particularly preferred.

Important compounds according to the invention are those of formula (I) in which R^1 is an isopropyl group, R^2 is a methyl group and OR^3 is a hydroxy, acetoxy, or methoxycarbonyloxy group.

As indicated previously, the compounds according to the invention may be of use as antibiotics. The compounds of the invention may also be of use as intermediates for the preparation of other active compounds. When the compounds of the invention are to be used as intermediates, the $-OR^3$ group may be a protected hydroxyl group and the invention particularly includes such protected compounds. It will be appreciated that such a group should have the minimum of additional functionality to avoid further sites of reaction and should be such that it is possible to selectively regenerate a hydroxyl group from it. Examples of protected hydroxyl groups are well known and are described, for example, in "Protective Groups in Organic synthesis" by Theodora W. Greene. (Wiley-Interscience, New York 1981) and "Protective Groups in Organic Chemistry" by J F W McOmie (Plenum Press, London, 1973). Examples of OR^3 protected hydroxy groups include phenoxyacetoxy, silyloxyacetoxy, (e.g. trimethylsilyloxyacetoxy and t-butyldimethylsilyloxyacetoxy), and silyloxy such as trimethylsilyloxy and t-butyldimethylsilyloxy. Compounds of the invention containing such groups will primarily be of use as intermediates. Other groups, such as acetoxy, may serve as protected hydroxyl groups, but may also be present in final active compounds.

Compounds of the invention have antibiotic activity e.g. antihelminthic activity, for example against nematodes, and in particular, anti-endoparasitic and anti-ectoparasitic activity.

Ectoparasites and endoparasites infect humans and a variety of animals and are particularly prevalent in farm animals such as pigs, sheep, cattle, goats and poultry (e.g. chickens and turkeys), horses, rabbits, game-birds, caged birds, and domestic animals such as dogs, cats, guinea pigs, gerbils and hamsters. Parasitic infection of livestock, leading to anaemia, malnutrition and weight loss is a major cause of economic loss throughout the world.

Examples of genera of endoparasites infecting such animals and/or humans are *Ancylostoma, Ascaridia, Ascaris, Aspicularis, Brugia, Bunostomum, Capillaria, Chabertia, Cooperia, Cyathostomes, Dictyocaulus, Dirofilaria, Dracunculus, Enterobius, Castrophilus, Haemonchus, Heterakis, Hyostrongylus, Loa, Metastrongylus, Necator, Nematodirus, Nematospiroides, Nippostrongylus, Oesophagostomum, Onchocerca, Ostertagia, Oxyuris, Parafilaria, Parascaris, Probstmayria, Strongylus, Strongyloides, Syphacia, Thelazia, Toxascaris, Toxocara, Trichonema, Trichostrongylus, Trichinella, Trichuris, Triodontophorus, Uncinaria and Wuchereria.*

Examples of ectoparasites infecting animals and/or humans are arthropod ectoparasites such as biting insects, blowfly, fleas, lice, mites, sucking insects, ticks and other dipterous pests.

Examples of genera of such ectoparasites infecting animals and/or humans are *Ambylomma, Anopheles, Boophilus, Chorioptes, Culexpipiens, Culliphore, Demodex, Damalinia, Dermatobia, Haematobia, Haematopinus, Haemophysalis, Hyaloma, Hypoderma, Ixodes, Linognathus, Lucilia, Melophagus, Oestrus, Otobius, Otodectes, Psorergates, Psoroptes, Rhipicephalus, Sarcoptes, Solenopotes, Stomoxys* and *Tabanus.*

The compounds according to the invention have been found to be effective both *in vitro* and *in vivo* against a range of endoparasites and ectoparasites. The antibiotic activity of compounds of the invention may, for example, be demonstrated by their activity against free living nematodes e.g. *Caenorhabditis elegans* and *Nematospiroides dubius.*

An important active compound of the invention is that of formula (1) in which:
R^1 is a methyl group, R^2 is a methyl group and OR^3 is a methoxy group.

Another important active compound of the invention is that of formula (I) in which:
R^1 is an ethyl group, R^2 is a methyl group and OR^3 is a hydroxyl group.

A particularly important active compound of the invention is that of formula (1) in which:
R^1 is an isopropyl group, R^2 is a methyl group and OR^3 is a hydroxyl group.

The compound of formula (I) in which R^1 is an isopropyl group, R^2 is a methyl group and OR^3 is a hydroxyl group is active against a wide range of endoparasites and ectoparasites. For example, this compound has been found to be active *in vivo* against parasitic nematodes such as *Ascaris, Cooperia curticei, Cooperia oncophora, Cyathostomes, Dictyocaulus viviparus, Dirofilaria immitis, Gastrophilus, Haemonchus contortus, Nematodirus battus, Nematodirus helvetianus, Nematodirus spathiqer, Nematospiroides dubius, Nippostrongylus braziliensis, Oesophaostomum, Onchocerca gutturosa, Ostertagia circumcincta, Ostertagia ostertagi, Oxyuris equi, Parascaris*

equorum, Probstmayria, stronylus edentatus, Stongylus vulgaris, Toxocara canis, Trichostrongylus axei, Trichostrongylus vitrinus, Triodontophorus and Uncinaria stenocephala, and parasitic grubs, mange mites, ticks and lice such as *Ambylomma hebraeum, Anopheles stevensi, Boophilus dicolarartus, Boophilus microplus, Chorioptes ovis, Culexpipiens molestus, Damalinia bovis, Dermatobia, Haematopinus, Hypoderma, Linognathus vituli, Lucilia sericata, Psoroptes ovis, Rhipicephalus appendiculatus* and *Sarcoptes.*

Compounds of the invention are also of use in combating insect, acarine and nematode pests in agriculture, horticulture, forestry, public health and stored products. Pests of soil and plant crops, including cereals (e.g. wheat, barley, maize and rice), cotton, tobacco, vegetables (e.g. soya), fruit (e.g. apples, vines and citrus) as well as root crops (e.g. sugarbeet, potatoes) may usefully be treated. Particular examples of such pests are fruit mites and aphids such as *Aphis fabae, Aulacorthum circumflexum, Myzus persicae, Nephotettix cincticeps, Nilparvata lugens, Panonychus ulmi, Phorodon humuli, Phyllocoptruta oleivora, Tetranychus urticae* and members of the genera *Trialeuroides*; nematodes such as members of the genera *Aphelencoides, Globodera, Heterodera, Meloidogyne* and *Panagrellus*; lepidoptera such as *Heliothis, Plutella* and *Spodoptera*; grain weevils such as *Anthonomus grandis* and *Sitophilus granarius*; flour beetles such as *Tribolium castaneum*; flies such as *Musca domestica*; fire ants; leaf miners; *Pear psylla; Thrips tabaci*; cockroaches such as *Blatella germanica* and *Periplaneta americana* and mosquitoes such as *Aedes aegypti.*

In particular, we have found that the compound of formula (1) in which R^1 is an isopropyl group, R^2 is a methyl group and OR^3 is a hydroxyl group is active against *Tetranychus urticae* (supported on french bean leaf), *Myzus persicae* (supported on chinese cabbage leaf), *Heliothis virescens* (supported on cotton leaf), *Nilaparvata lugens* (supported on rice plant), *Musca domestica* (in a plastic pot with cotton wool/sugar solution), *Blattella germanica* (in a plastic pot with food pellets), *Spodoptera exigua* (supported on a cotton leaf) and *Meloidogyne incognita.*

Compounds of the invention may also be of use as anti-fungals, for example, against strains of *Candida* sp. such as *Candida albicans* and *Candida glabrata* and against yeast such as *Saccharomyces carlsbergensis.*

According to the invention we therefore provide compounds of formula (1) as defined above, which may be used as antibiotics. In particular, they may be used in the treatment of animals and humans with endoparasitic, ectoparasitic and/or fungal infections and in agriculture, horticulture, or forestry as pesticides to combat insect, acarine and nematode pests. They may also be used generally as pesticides to combat or control pests in other circumstances, e.g. in stores, buildings or other public places or location of the pests. In general the compounds may be applied either to the host (animal or human or plants or vegetation) or a locus thereof or to the pests themselves.

Compounds of the invention may be formulated for administration in any convenient way for use in veterinary or human medicine and the invention therefore includes within its scope pharmaceutical compositions comprising a compound in accordance with the invention adapted for use in veterinary or human medicine. Such compositions may be presented for use in conventional manner with the aid of one or more suitable carriers or excipients. The compositions of the invention include those in a form especially formulated for parenteral (including intramammary administration), oral, rectal, topical, intraruminal, implant, ophthalmic, nasal or genito-urinary use.

The compounds according to the invention may be formulated for use in veterinary or human medicine by injection and may be presented in unit dose form, in ampoules, or other unit-dose containers, or in multi-dose containers, if necessary with an added preservative. The compositions for injection may be in the form of suspensions, solutions, or emulsions, in non-aqueous or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, emulsifying, solubilising and/or dispersing agents. Alternatively the active ingredient may be in sterile powder form for reconstitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. Oily vehicles include polyhydric alcohols and their esters such as glycerol esters, fatty acids, vegetable oils such as arachis oil, cottonseed oil or fractionated coconut oil, mineral oils such as liquid paraffin, isopropyl myristate and ethyl oleate and other similar compounds. Other vehicles containing materials such as glycerol formal, propylene glycol, polyethylene glycols, ethanol or glycofurol may also be used. Conventional non-ionic, cationic or anionic surface active agents may be used alone or in combination in the composition.

Compositions for veterinary medicine may also be formulated as intramammary preparations in either long acting or quick-release bases and may be sterile solutions or suspensions in aqueous or oily vehicles optionally containing a thickening or suspending agent such as soft or hard paraffins, beeswax, 12-hydroxy stearin, hydrogenated castor oil, aluminium stearates, or glyceryl monostearate. Conv ntional non-ionic, cationic or anionic surface active agents may be used alone or in combination in the composition.

The compounds of the invention may also be pres nted for veterinary or human use in a form suitable for oral administration, for example in the form of solutions, syrups, emulsions or

suspensions, or a dry powder for constitution with water or other suitable vehicle before use, optionally with flavouring and colouring agents. Solid compositions such as tablets, cspsules, lozenges, pills, boluses, powder, pastes, granules, bullets or premix preparations may also be used. Solid and liquid compositions for oral use may be prepared according to methods well known in the art. Such compositions may also contain one or more pharmaceutically acceptable carriers and excipients which may be in solid or liquid form. Examples of suitable pharmaceutically acceptable carriers for use in solid dosage forms include binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). Tablets may be coated by methods well known in the art.

Examples of suitable pharmaceutically acceptable additives for use in liquid dosage forms include suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl p-hydroxybenzoates or sorbic acid); stabilising and solubilising agents may also be included.

Pastes for oral administration may be formulated according to methods well known in the art. Examples of suitable pharmaceutically acceptable additives for use in paste formulations include suspending or gelling agents e.g. aluminium distearate or hydrogenated castor oil; dispersing agents e.g. polysorbates; non-aqueous vehicles e.g. arachis oil, oily esters, glycols or macrogols; stabilising and solubilising agents. The compounds of the invention may also be administered in veterinary medicine by incorporation thereof into animals daily solid or liquid dietary intake, e.g. as part of the daily animal feed or drinking water.

The compounds of the invention may also be administered orally in veterinary medicine in the form of a liquid drench such as a solution, suspension or dispersion of the active ingredient together with a pharmaceutically aceptable carrier or excipient.

The compounds of the invention may also, for example, be formulated as suppositories e.g. containing conventional suppository bases for use in veterinary or human medicine or as pessaries e.g. containing conventional pessary bases.

Compounds according to the invention may be formulated for topical administration, for use in veterinary and human medicine, as ointments, creams, lotions, shampoos, powders, sprays, dips, aerosols, drops (e.g. eye or nose drops) or pour-ons. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components. Pour-ons may, for example, be formulated for veterinary use in organic solvents or as an aqueous suspension, and may include agents which promote percutaneous adsorption, and formulation agents which solubilise, stabilise, preserve or otherwise improve the storage properties and/or ease of application.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Powders may be formed with the aid of any suitable powder base. Drops may be formulated with an aqueous or non aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

For administration by inhalation the compounds according to the invention may be delivered for use in veterinary or human medicine in the form of an aerosol spray presentation or an insufflator.

The total daily dosages of compounds of the invention employed in both veterinary and human medicine will suitably be in the range 1-2000μg/kg bodyweight, preferably from 5-800μg/kg and these may be given in divided doses, e.g. 1-4 times per day. It will be appreciated that the dosage will vary according to the age and condition of the patient, the organism being treated, the mode of administration and the particular composition formulated. Dosages for a given host can be determined using conventional considerations, eg. by comparison of the activities of the subject compound and of a known antibiotic agent.

Th compounds according to th invention may be formulated in any convenient way for horticultural or agricultural use and the invention therefore includes within its scope compositions comprising a compound according to the invention adapted for horticultural or agricultural use. Such formulations include dry or liquid types, for example dusts, including dust bases or concentrates, powders, including soluble or wettable powders, granulates, including microgranules and dispersible granules, pellets, flowables, emulsions such as dilute emulsions or emulsifiable concentrates, dips such as root dips and seed dips, seed dressings, seed pellets, oil concentrates, oil solutions, injections e.g. stem injections, sprays, smokes and mists.

G nerally such formulations will include the compound in association with a suitable carrier or diluent. Such carriers may be liquid or solid and designed to aid the application of the compound eith r by way of dispersing it where it is to be applied or to provide a formulation which can be

made by the user into a dispersible preparation. Such formulations are well known in the art and may be prepared by conventionsl methods such as, for example by blending and/or grinding of the active ingredient(s) together with the carrier or diluent, e.g. solid carrier, solvent or surface active agent.

Suitable solid carriers, for use in the formulations such as dusts, granulates and powders may be selected from for example natural mineral fillers, such as diatomite, talc, kaolinite, montmorillonite prophyllite or attapulgite. Highly dispersed silicic acid or highly dispersed absorbent polymers may, if desired, be included in the composition. Granulated adsorptive carriers which may be used may be porous (such as pumice, ground brick, sepiolite or bentonite) or non-porous (such as calcite or sand). Suitable pregranulated materials which may be used and which may be organic or inorganic include dolomite and ground plant residues.

Suitable solvents for use as carriers or diluents include aromatic hydrocarbons, aliphatic hydrocarbons, alcohols and glycols or ethers thereof, esters, ketones, acid amides, strongly polar solvents, optionally epoxidized vegetable oils and water.

Conventional non-ionic, cationic or anionic surface-active agents, e.g. ethoxylated alkyl phenols and alcohols, alkali metal or alkaline earth metal salts of alkyl benzene sulphonic acids, lignosulphonic acids or sulphosuccinic acids or sulphonates of polymeric phenols which have good emulsifying, dispersing and/or wetting properties may also be used either alone or in combination in the compositions.

Stabilizers, anti-caking agents, anti-foaming agents, viscosity regulators, binders and adhesives, photostabilisers as well as fertilizers, feeding stimulants or other active substances may, if desired, be included in the compositions. The compounds of the invention may also be formulated in admixture with other insecticides, acaricides and nematicides.

In the formulations, the concentration of active material is generally from 0.01 to 99% and more preferably between 0.01% and 40% by weight.

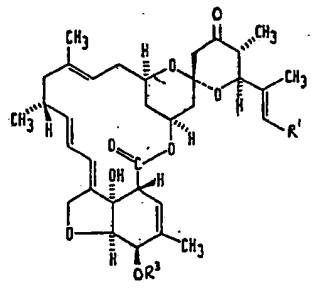
Commercial products are generally provided as concentrated compositions to be diluted to an appropriate concentration, for example from 0.001 to 0.0001% by weight, for use.

The rate at which a compound is applied depends upon a number of factors including the type of pest involved and the degree of infestation. However, in general, an application rate of 10g/ha to 10kg/ha will be suitable; preferably from 10g/ha to 1kg/ha for control of mites and insects and form 50g/ha to 10kg/ha for control of nematodes.

The compounds of the invention may be administered or used in combination with other active ingredients. In particular, the compounds of the invention may be administered or used in combination with other known anthelmintic agents. By combining the compounds of the invention with other anthelmintic agents the spectrum of parasitic infections which may be successfully combatted may be expanded. Thus, the possibility of eliminating parasitic infections against which the individual components are ineffective or only partially effective may be realised.

The compounds of the invention may be prepared by the processes discussed below. In some of these processes it may be necessary to protect a hydroxyl group at the 5-position in the starting material prior to effecting the reaction described. In such cases it may then be necessary to deprotect the same hydroxyl group once the reaction has occurred to obtain the desired compound of the invention. Conventional protection and deprotection methods may be used, for example as described in the aforementioned books by Greene and McOmie.

According to one aspect of the invention we provide a process (A) for the preparation of compounds of formula (1) which comprises reacting compounds of formula (II):



(II)

(where R^1 and OR^3 are as previously defined) with a reagent H_2NOR^2 or a salt thereof (where R^2 is as previously defined), and, if desired, followed by deprotection of a compound of formula (1) in which OR^3 is a protected hydroxyl group, and optionally followed by salt formation.

The oximation reaction may be effected in aqueous or non-aqueous reaction media, conveniently at a temperature in the range −20 to +100°C, e.g. −10 to +50°C. It is convenient to use the reagent H_2NOR^2 in the form of a salt, for example an acid addition salt such as the hydrochlorid . When such a salt is mployed the reaction may be carried out in the presence of an acid binding agent.

Solvents which may be employed include water and water miscible solvents such as alcohols (e.g. methanol or ethanol), amides (e.g. N,N-dimethylformamide, N,N-dimethylacetamide or hexamethylphosphoramide), ethers (e.g. cyclic ethers such as tetrahydrofuran or dioxan, and acylic ethers such as dimethoxyethane or diethylether), nitriles (e.g. acetonitrile), sulphones (e.g. sulpholane), hydrocarbons such as halogenated hydrocarbons (e.g. methylene chloride), and esters such as ethyl acetate, as well as mixtures of two or more such solvents.

When aqueous conditions are employed the reaction may conveniently be buffered to pH 2-9 with an appropriate acid, base or buffer.

Suitable acids include mineral acids, such as hydrochloric or sulphuric acid, and carboxylic acid such as acetic acid. Suitable bases include alkali metal carbonates and bicarbonates such as sodium bicarbonate, hydroxides such as sodium hydroxide, and alkali metal carboxylates such as sodium acetate. A suitable buffer is sodium acetate/acetic acid.

Compounds of formula (II) are either known compounds described in UK Patent Specification 2176182 or may be prepared from known compounds described therein using standard procedures.

According to a further aspect of the invention we provide a further process (B) for the preparation of compounds of formula (1) in which R^2 is a C_{1-8} alkyl or C_{3-8} alkenyl group and OR^3 is a substituted hydroxyl group which comprises reacting a compound of formula (1) in which OR^3 is a hydroxyl group with a reagent serving to convert a hydroxyl group into a substituted hydroxyl group, optionally followed by salt formation.

Acylation, formylation, sulphonylation, etherification, silylation or acetal formation reactions may be carried out by conventional methods as described below.

Thus, for example, acylation may be effected using an acylating agent such as an acid of formula R^4COOH or a reactive derivative thereof, such as an acid halide (e.g. acid chloride), anhydride or activated ester, or a reactive derivative of a carbonic acid R^4OCOOH or thiocarbonic acid R^4OCSOH.

Acylations employing acid halides and anhydrides may if desired be effected in the presence of an acid binding agent such as a tertiary amine (e.g. triethylamine, dimethylaniline or pyridine), inorganic bases (e.g. calcium carbonate or sodium bicarbonate), and oxiranes such as lower 1,2-alkylene oxides (e.g. ethylene oxide or propylene oxide) which bind hydrogen halide liberated in the acylation reaction.

Acylations employing acids are desirably conducted in the presence of a condensing agent, for example a carbodiimide such as N,N'-dicyclohexylcarbodiimide or N-ethyl-N'γ-dimethylaminopropylcarbodiimide; a carbonyl compound such as carbonyldiimidazole; or an isoxazolium salt such as N-ethyl-5-phenylisoxazolium perchlorate.

An activated ester may conveniently be formed *in situ* using, for example, 1-hydroxybenzotriazole in the presence of a condensing agent as set out above. Alternatively, the activated ester may be preformed.

The acylation reaction may be effected in aqueous or non-aqueous reaction media, conveniently at a temperature in the range $-20°$ to $+100°C$, e.g. $-10°$ to $+50°C$.

Formylation may be effected using an activated derivative of formic acid e.g. N-formyl imidazole or formic acetic anhydride under standard reaction conditions.

Sulphonylation may be effected with a reactive derivative of a sulphonic acid R^6SO_3H such as a sulphonyl halide, for example a chloride R^6SO_2Cl or a sulphonic anhydride. The sulphonylation is preferably effected in the presence of a suitable acid binding agent as described above.

Etherification may be effected using a reagent of formula R^5Y (where R^5 is as previously defined and Y represents a leaving group such as chlorine, bromine or iodine atom or a hydrocarbylsulphonyloxy group, such as mesyloxy or tosyloxy, or a haloalkanoyloxy group such as dichloroacetoxy). The reaction may be carried out by formation of a magnesium alkoxide using a Grignard reagent such as a methylmagnesium halide e.g. methylmagnesium iodide or using a trialkylsilylmethylmagnesium halide e.g. trimethylsilylmethylmagneaium chloride followed by treatment with the reagent R^5Y.

Alternatively, the reaction may be effected in the presence of a silver salt such as silver oxide, silver perchlorate, silver carbonate or silver salicylate or mixtures thereof, and this system may be particularly appropriate when etherification is carried out using an alkyl halide (e.g. methyl iodide).

Etherification may conveniently be effected in a solvent such as an ether e.g. diethyl ether.

Acetal formation may be carried out by reaction with a cyclic or acyclic vinyl ether. This method is especially us ful for production of tetrahydropyranyl ethers, using dihydropyran as reagent, or 1-alkoxyalkyl ethers such as 1-ethoxyalkyl ether, using an alkyl vinyl ether as reagent. The reaction is desirably carried out in the presence of a strong acid catalyst, for example a mineral acid such as sulphuric acid, or an organic sulphonic acid such as p-toluene sulphonic acid, in a non-hydroxylic, substantially water-fr e solvent.

Solvents which may be employed in the above reactions include ketones (e.g. acetone), amides (e.g. N,N-dimethylformamide, N,N-dimethylacetamide or hexamethylphosporamide), ethers

(e.g. cyclic ethers such as tetrahydrofuran or dioxan, and acyclic ethers such as dimethoxyethane or diethylether), nitriles (e.g. acetonitrile), hydrocarbons such as halogenated hydrocarbons (e.g. methylene chloride), and esters such as ethyl acetate, as well as mixtures of two or more such solvents.

Silylation may be effected by reaction with a silyl halide (e.g. chloride), advantageously in th presence of a base such as imidazole triethylamine or pyridine, using a solvent such as dimethylformamide.

Carbamoylation to provide a compound of formula (I) in which OR^3 is a group $OCONR^8R^9$ may be effected by reaction with a suitable acylating (ie carbamoylating) agent. Suitable carbamoylating agents which may be used to afford compounds in which one of R^8 and R^9 is a hydrogen atom and the other is a C_{1-4} alkyl group include isocyanates of formula $R^{10}NCO$ (wherein R^{10} is a C_{1-4}alkyl group). The carbamoylation reaction may desirably be effected in the presence of a solvent or solvent mixture selected from hydrocarbons (e.g. aromatic hydrocarbons such as benzene and toluene), halogenated hydrocarbons (e.g. dichloromethane), amides (e.g. formamide or dimethylformamide), esters (e.g. ethyl acetate), ethers (e.g. cyclic ethers such as tetrahydrofuran and dioxan), ketones (e.g. acetone), sulphoxides (e.g. dimethylsulphoxide) or mixtures of these solvents. The reaction may conveniently be carried out at a temperature of between −80°C and the boiling temperature of the reaction mixture, for example up to 100°C, preferably between −20° and +30°C.

The carbamoylation may be assisted by the presence of a base, e.g. a tertiary organic base such as tri-(lower alkyl)amine (e.g. triethylamine).

Another useful carbamoylating agent is cyanic acid, which is conveniently generated *in situ*, for example, from an alkali metal cyanate such as sodium cyanate, the reaction being facilitated by the presence of an acid, e.g. a strong organic acid such as trifluoroacetic acid. Cyanic acid effectively corresponds to the isocyanate compounds mentioned above wherein R^{10} is hydrogen and therefore converts compounds of formula (II) directly to their carbamoyloxy analogues (i.e. compounds of formula (I) in which OR^3 is a group $OCONH_2$).

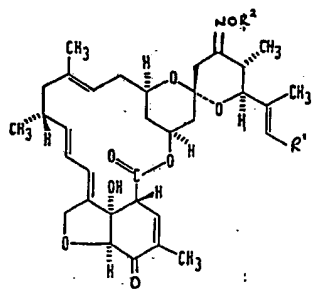
Alternatively, carbamoylation may be effected by reaction with phosgene or carbonyldiimidazole followed by ammonia or the appropriate substituted amine, optionally in an aqueous or non-aqueous reaction medium.

The formation of compounds of formula (1) in which OR^3 represents a group $OCO(CH_2)_nCO_2R^7$ may be achieved by acylation of the corresponding 5-hydroxy compound with an acid $HO_2C(CH_2)_nCO_2R^7$ or a reactive derivative thereof according to the acylation procedure described above.

According to another aspect of the invention we provide a further process (C) for the prepsration of compounds of formula (1) in which R^2 is a C_{1-8} alkyl or C_{3-8} alkenyl group which comprises reacting a compound of formula (I) in which R^2 is a hydrogen atom and OR^3 is a substituted hydroxyl group with an etherifying agent R^2Y (where R^2 is a C_{1-8} alkyl or C_{3-8} alkenyl group and Y is as previously defined), and if desired followed by deprotection of a compound of formula (I) in which OR^3 is a protected hydroxyl group, and optionally followed by salt formation.

The etherification resction may be carried out, for example, by formation of a magnesium alkoxide using a Grignard reagent such as a methylmagnesium halide e.g. methylmagnesium iodide followed by treatment with the reagent R^2Y. Alternatively, the reaction may be effected in the presence of a silver salt such as silver oxide, silver perchlorate, silver carbonate or silver salicylate or mixtures thereof or in the presence of a base e.g. potassium carbonate or sodium hydride. Etherification may conveniently be carried out in an organic solvent such as an ether e.g. diethyl ether, tetrahydrofuran or dioxan or an amide e.g. dimethylformamide or hexamethylphosphoric triamide or a mixture of such solvent at ambient temperature. Under these conditions the configuration of the oximino group is substantially unchanged by the etherification reaction.

According to another aspect of the invention we provide a yet further process (D) for the preparation of compounds of formula (1) in which OR^3 is a hydroxyl group which comprises reducing a compound of formula (III)



(III)

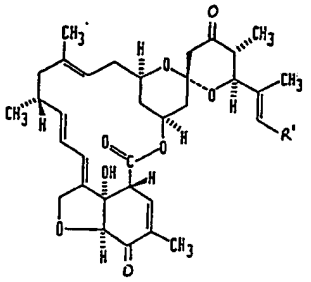
and optionally followed by salt formation.

The reduction may be effected with a reducing agent which is capable of stereoselectively

reducing the 5-keto group. Suitable reducing agents include borohydrides such as alkali metal borohydrides (e.g. sodium borohydride) and lithium alkoxyaluminium hydrides such as lithium tributoxyaluminium hydride.

The reaction involving a borohydride reducing agent takes place in the presence of a solvent such as an alkanol e.g. isopropyl alcohol or isobutyl alcohol conveniently at a temperature in the range of −30° to +80°C e.g. at 0°C. The reaction involving a lithium alkoxyaluminium hydride takes place in the presence of a solvent such as an ether e.g. tetrahydrofuran or dioxan conveniently at a temperature in the range of −78° to 0°C.

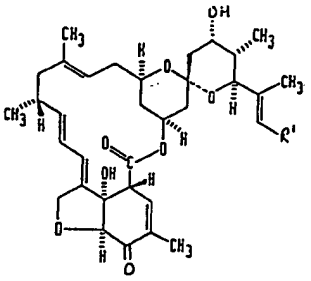
Intermediate compounds of formula (III) may be prepared from a 5,23-diketone of formula (IV)



(IV)

by treatment with one equivalent of a reagent H_2NOR^2 (where R^2 is as previously defined) using the oximation conditions described above for the preparation of compounds of formula (1).

Compounds of formula (IV) may be prepared by oxidising a compound of formula (V)



(V)

The reaction may be effected with an oxidising agent serving to convert a secondary hydroxyl group to an oxo group, whereby a compound of formula (IV) is produced.

Suitable oxidising agents include quinones in the presence of water, e.g. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone or 2,3,5,6 tetrachloro-1,4-benzoquinone; a chromium (VI) oxidising agent, e.g. sodium or pyridinium dichromate or chromium trioxide in pyridine preferably in the presence of a phase transfer catalyst; a manganese (IV) oxidising agent, e.g. manganese dioxide in dichloromethane; an N-halosuccinimide, e.g. N-chlorosuccinimide or N-bromosuccinimide; a dialkylsulphoxide e.g. dimethylsulphoxide, in the presence of an activating agent such as N,N'-dicyclohexylcarbodiimide or an acyl halide, e.g. oxalyl choride; or a pyridine-sulphur trioxide complex.

The reaction may conveniently be effected in a suitable solvent which may be selected from a ketone, e.g. acetone; an ether, e.g. diethyl ether, dioxan or tetrahydrofuran; a hydrocarbon, e.g. hexane; a halogenated hydrocarbon e.g. chloroform or methylene chloride; or an ester, e.g. ethyl acetate or a substituted amide e.g. dimethylformamide. Combinations of such solvents either alone or with water may also be used. The choice of solvent will depend upon the type of oxidising agent used for the conversion.

The reaction may be carried out at a temperature of from −80°C to +50°C.

The compounds of formula (V) may be prepared, for example, by cultivating *Streptomyces thermoarchaensis* NCIB 12015 (deposited 10th September 1984 in the p rmanent culture collection of the National Collections of Industrial and Marine Bacteria, Torry Research Station, Aberdeen, United Kingdom) or a mutant thereof and isolating the compound from the fermentation broth so obtained.

The *Streptomyces* organism may be cultured by conventional means, i.e. in the presence of assimilable sources of carbon, nitrogen and mineral salts. Assimilable sources of carbon, nitrogen and minerals may be provided by either simple or complex nutrients for example as described in UK Patent Specification 2166436. Suitable media comprising these are described in Preparation 1 hereinafter.

Cultivation of the *Streptomyces* organism will gen rally be effected at a t mperature of from 20 to 50°C preferably from 25 to 40°C, and will desirably take place with aeration and agitation

e.g. by shaking or stirring. The medium may initially be inoculated with a small quantity of a sporulated suspension of the microorganism but in order to avoid a growth lag a vegetative inoculum of the organism may be prepared by inoculating a small quantity of the culture medium with the spore form of the organism, and the vegetative inoculum obtained may be transferred to the fermentation medium, or, more preferably to one or more seed stages where further growth takes place before transfer to the principal fermentation medium. The fermentation will generally be carried out in the pH range 5.5 to 8.5.

The fermentation may be carried out for a period of 2-10 days, e.g. about 5 days.

The compounds of formula (V) may be separated from the whole fermentation broth so obtained by conventional isolation and separation techniques. A variety of fractionation techniques may be used, for example adsorption-elution, precipitation, fractional crystallisation and solvent extraction which may be combined in various ways. Solvent extraction and chromatography have been found to be most suitable for isolating and separating the compound. A suitable method for obtaining the compounds of formula (V) using these procedures is described in Preparation 1 hereinafter.

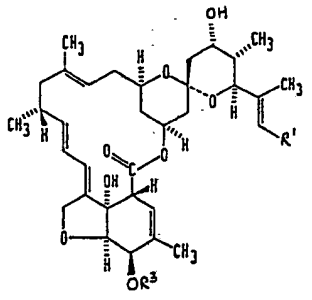
According to another aspect of the invention we provide a further process (E) for the preparation of compounds of formula (I) in which OR^3 is a hydroxyl group which comprises deprotecting a corresponding compound of formula (I) in which OR^3 is a protected hydroxyl group as described above.

Thus, for example, an acyl group such as an acetyl group may be removed by basic hydrolysis e.g. using sodium or potassium hydroxide in aqueous alcohol or by acid hydrolysis e.g. using concentrated sulphuric acid in methanol. Acetal groups such as tetrahydropyranyl may be removed for example, using acid hydrolysis (using an acid such as acetic or trifluoroacetic acid or a dilute mineral acid). Silyl groups may be removed using fluoride ions (e.g. from a tetraalkylammonium fluoride such as tetra-*n*-butylammonium fluoride), hydrogen fluoride in aqueous acetonitrile or an acid such as *p*-toluene sulphonic acid (e.g. in methanol). Arylmethyl groups may be removed by treatment with a Lewis acid (e.g. boron trifluoride-etherate) in the the presence of a thiol (e.g. ethanethiol) in a suitable solvent such as dichloromethane at e.g. room temperature.

Salts of acids of formula (I) may be prepared by conventional methods, for example by treating the acid with a base or converting one salt into another by exchange of ion.

The invention is illustrated but not limited by the following Preparations and Examples in which temperatures are in °C, 'L' represents litre and EtOH represents ethanol.

In the following Preparations and Examples compounds are named as derivatives of the known 'Factors', Factors A, B, C and D. Factor A is a compound of formula (VI) in which R^1 is isopropyl and R^3 is hydrogen; Factor B is a compound of formula (VI) in which R^1 is methyl and R^3 is methyl; Factor C is a compound of formula (VI) in which R^1 is methyl and R^3 is hydrogen; and Factor D is a compound of formula (VI) in which R^1 is ethyl and R^3 is hydrogen.



(VI)

Preparation 1- 5-Keto Factor A

Spores of *Streptomyces thermoarchaensis* NCIB 12015 were inoculated onto agar slants made up of the following ingredients

	gL^{-1}
Yeast extract (Oxoid L21)	0.5
Malt extract (Oxoid L39)	30.0
Mycological peptone (Oxoid L40)	5.0
Agar No. 3 (Oxoid L13)	15.0
Distilled water to 1 L	
pH ~ 5.4	

and incubated at 28° for 10 days.

The mature slant was then covered with 6ml of a 10% glycerol solution and scraped with a sterile tool to loosen the spores and mycelium. 0.4ml aliquots of the resulting spore suspension were transferred to sterile polypropylene straws which were then heat-sealed and stored in liquid nitrogen vapour until required.

Two 250ml Erlenmeyer flasks containing 50ml of seed medium made up as follows:

	gL^{-1}
D-Glucose	15.0
Glycerol	15.0
Soya peptone	15.0
NaCl	3.0
$CaCO_3$	1.0
Distilled water to 1 L	

[The unadjusted pH of the medium was 6.7 which was adjusted to pH 7.0 with aqueous sodium hydroxide before autoclaving. The pH of the medium after autoclaving was 7.3]

were each inoculated with 0.2ml of the spore suspension taken from a straw.

The flasks were incubated at 28° for 3 days on a shaker rotating at 250rpm with a 50mm diameter orbital motion.

The contents of both flasks were used to inoculate a 70 L fermenter vessel containing 40 L of the same medium supplemented with polypropylene 2000 (0.06% v/v). Polypropylene 2000 was added as required throughout the fermentation to control foaming. The fermentation was carried out at 28°, with agitation and aeration sufficient to maintain a dissolved oxygen level of greater than 30% saturation. After 24 h of fermentation, a 9 L portion of broth was transferred to a 700 L fermenter containing 450 L of medium made up as follows:

	gL^{-1}
D-glucose	2.8
Malt Dextrin (MD30E)	27.8
Arkasoy 50	13.9
Molasses	1.7
K_2HPO_4	0.14
$CaCO_3$	1.39
Silicone 525 (Dow Corning)	0.06% (v/v)

Adjusted to pH 6.5 before sterilisation.

The fermentation was carried out at 28° with agitation and aeration. Polypropylene 2000 antifoam was added as required and the pH was kept down to pH 7.2 by the addition of H_2SO_4 until harvest. The fermentation was harvested after 5 days.

Th broth (450 L) was clarifi d on a Westfalia KA 25 centrifuge and the residual supernatant

was displaced with water (20 L). The recovered cells (25.5 kg) were stirred for 1 h with a Silverson mixer model BX in sufficient methanol to give a total volume of 75 L. The suspension was filtered and the solid residue was re-extracted with methanol (35 L) and filtered. The combined filtrate (87 L) was diluted with water (40 L) and extracted with 60°-80° petroleum ether (30 L). After 30 min. the phases were separated on a Westfalia MEM 1256 centrifuge and the lower methanol phase was re-extracted with 60°-80° petroleum ether (30 L) after the addition of water (40 L). After separation the lower phase was again extracted with 60°-80° petroleum ether (30 L). The combined petroleum ether phases (85 L) were concentrated by three passes through a Pfaudler 8.8-12v-27 wiped-film evaporator (vapour pressure 0.1 bar, vapour temperature 20°, steam temperature 127°). The concentrate (9 L) was dried with sodium sulphate (2 kg) and further concentrated under reduced pressure at 40° in a rotary film evaporator.

The oily residue (130g) was dissolved in chloroform to give 190ml and this was applied to a column of Merck 7734 silica 60 (200×4cm) packed in chloroform. The column was washed with chloroform (500ml) and eluted with chloroform:ethyl acetate (3:1) and fractions of approximately 40ml were collected after a forerun of 1,400ml.

Fractions 32-46 were combined and evaporated to yield an oil (21.2g). Fractions 47-93 were combined and evaporated to give an oil (20.1g) which was dissolved in chloroform:ethyl acetate (3:1) to 50ml, and applied to a column of Merck 7734 silica 60 (200×4cm) packed in chloroform:ethyl acetate (3:1), and fractions of approximately 40mls were collected after a forerun of 1,400 ml. Fractions 22-36 were combined and evaporated to give an oil (3.1g) which was added to the oil obtained from fractions 32-46 from the first column. The combined oils were dissolved in boiling methanol (4ml) which was then added to hot propan-2-ol (20ml) and allowed to crystallise.

Mother liquor after crystallisation was evaporated to yield an oil which was dissolved in an equal volume of methylene chloride and loaded onto a column (30×2.2cm) of Merck Kieselgel 60 (70-230 mesh ASTM, Art. No. 7734) packed in methylene chloride. The bed was washed with methylene chloride (2 bed volumes) and eluted with chloroform:ethyl acetate (3:1) (2 bed volumes). Evaporation of the eluate yielded an oil which was dissolved in methanol and subjected to preparative high performance liquid chromatography (hplc) on Spherisorb S5 ODS-2 (250mm×20mm, Phase Sep.Ltd.). Portions of the sample (5ml) were pumped onto the column over a period of 1 minute and the column was eluted with acetonitrile:water (7:3) under the following conditions:

Time (mins)	Flow (ml/min)	
0.00	0.00	) Injection
1.00	0.00	) time
1.10	30.00	
39.90	30.00	
40.00	35.00	
75.00	35.00	

Material eluting from the hplc column was monitored by uv spectroscopy at 238nm.

Evaporation of the combined fractions with peaks eluting at 33.4 minutes yielded the *title compound* (34mg) as a solid.

E.I. mass spectroscopy yielded a molecular ion at 610 and gave characteristic fragments at :
592
574
556
422
259
241

Example 1

23[E]-Methoxyimino Factor A

(a) *5,23-Diketo Factor A*

An ice-cold solution prepared from concentrated sulphuric acid (1.2ml) and sodium dichromate (120mg) in water (2ml) was added ov r 15 min to an ic -cold solution of 5-keto Factor A (200mg) and tetrabutylammonium hydrogen sulphate (15mg) in ethyl acetate (4ml) with vigorous stirring. After 1h the mixture was diluted with ethyl acetate and the organic phase was washed with saturated aqueous sodium bicarbonate. The dried organic phase was evaporated and the

gum was purified by chromatography over Merck Keiselgel 60 230-400 mesh (100ml). Elution with 10% ethyl acetate in dichloromethane afforded the *title compound* as a pale yellow foam (86mg) δ ($CDCl_3$) includes 6.57 (m,1H); 2.50 (s,2H); and 1.89 (m,3H).

(b) *5-Keto, 23[E]-methoxyimino Factor A*

5,23-Diketo Factor A (475mg), methoxylamine hydrochloride (69mg) and anhydrous sodium acetate (135mg) were dissolved in methanol. After 1.5h at room temperature, the solution was kept at −18° for 16h, diluted with ethyl acetate and washed successively with 1N hydrochloric acid, water, and brine. The dried organic phase was evaporated and the yellow foam was purified by chromatography over Merck Keiselgel 60, 230-400 mesh (120ml). Elution of the column with hexane:ethyl acetate (4:1) afforded the *title compound* as a yellow foam (255mg) $[a]_D^{21}$ + 80° (*c* 1.20, $CHCl_3$), λ_{max} (EtOH) 241nm (ε 27,500), ν_{max} ($CHBr_3$), 3530, 3460 (OH) 1708 (C=O), 1676 (C=C−C=O), 986 (C-O) δ ($CDCl_3$) includes 6.58 (s;1H), 3.84 (s;4H), 3.80 (s;1H), 3.58 (m;1H), 3.30 (d14;1H), 1.00 (d6;3H), 0.96 (d6;3H), 0.92 (d6;3H).

(c) *23[E]-Methoxyimino Factor A*

(i) Sodium borohydride (6.5mg) was added to an ice-cold solution of 5-keto, 23[E]-methoxyimino Factor A (83mg) in isopropanol (20ml). The yellow mixture was stirred for 35 min in an ice-bath, diluted with ethyl acetate and washed successively with 1N hydrochloric acid, water and brine. The dried organic phase was evaporated and the resultant yellow gum was purified by chromatography over Merck Keiselgel 60, 230-400 mesh (60ml). Elution of the column with hexane:ethyl acetate (2:1) afforded the *title compound* as a yellow foam (58mg). Crystallisation from hexane afforded the *title compound*, m.p. 203° $[\alpha]_D^{21}$ + 133° (*c* 1.12, $CHCl_3$), λ_{max} (EtOH) 244nm (ε 26,200), δ ($CDCl_3$) includes 4.29 (t7;1H), 3.84 (s;3H), 3.29 (d15;1H).

(ii) A solution of 5-keto, 23[E]-methoxyimino Factor A (50 mg) in dry tetrahydrofuran (1 ml) was added to a cooled (−78°) solution of lithium tris-t-butoxyaluminium hydride (261 mg) in dry tetrahydrofuran (3 ml). After 0.75 h at −78°, the solution was diluted with ethyl acetate (30 ml) and washed successively with 0.5N hydrochloric acid and water. The dried organic phase was evaporated and the crude product was purified by chromatography over Merck kieselgel 60, 230-400 mesh (40 ml), eluting with 25 % ethyl acetate in hexane to afford the *title compound* as a white foam, $[\alpha]_D^{21}$ + 128° (*c* 0.95, $CHCl_3$), δ($CDCl_3$) includes 4.29 (t7;1H), 3.84(s;3H), 3.29(d15;1H).

Example 2

23[E]-Methoxyimino Factor A, 5-acetate

A solution of anhydrous sodium acetate (2.8g) in water (15 ml) was added to a solution of 23-keto Factor A,5-acetate (3.13g, Example 18 in UK Patent Specification 2176182) in methanol, followed by methoxyamine hydrochloride (3.01g). The resultant solution was stirred for 1.5h at 20°, diluted with ethyl acetate then washed successively with 0.5N hydrochloric acid, water and brine. The dried organic phase was evaporated to near dryness and the off-white foam was purified by chromatography over Merck Kieselgel 60 230-400 mesh (600 ml). Elution of the column with hexane: ethyl acetate (4:1) afforded the *title compound* as a colourless foam (2.14g) $[\alpha]_D^{21}$ + 128° (*C* 1.35, $CHCl_3$) λ_{max} (EtOH) 244nm (ε_{max} 27,250); ν_{max} ($CHBr_3$) 3560, 3480 (OH), 1733 (acetate), 1715 (C=O), 995 (C−O), δ($CDCl_3$) include 5.5-5.6 (m:2H), 3.84 (S:3H) 3.29 (d 15;H), 2.16 (S:3H).

Example 3

23[E]-Hydroxyimino Factor A,5-acetate

Reaction of 23-keto Factor A,5-acetate with hydroxylamine hydrochloride was effected in a manner similar to that described in Example 1 above. The crude product was purified by chromatography over Merck Kieselgel 60 230-400 mesh, eluting with ethyl acetate:. acetonitrile (4:1) to afford the *title compound* as a colourless foam $[\alpha]_D^{21}$ + 132° (c 1.01, $CHCl_3$), λ_{max} (EtOH) 244nm (ε_{max} 27800), ν_{max} ($CHBr_3$) 3565, 3470 (OH), 1732 (acetate), 1712 (C=O), 993 (C−O), δ($CDCl_3$) include 8.12 (S;1H), 5.5-5.6 (m:2H), 3.42 (d 15:1H), 2.16 (5:3H).

Example 4

23[E]-Methoxyimino Factor A

A solution of the product of Example 2 (1.88 g) in methanol was cooled in an ice bath, 1N aqueous sodium hydroxide (5.6 ml) was added, and the solution was stirred in an ice bath for 1.5h. The solution was diluted with ethyl acetate and washed successively with 0.5N aqueous hydrochloric acid, water and brine. The dried organic phase was evaporated and the resultant foam was purified by chromatography over Merck Kieselgel 60 230-400 mesh (400 ml). Elution of the column with hexane: ethyl acetate (2:1) afforded a colourless foam (1.429g) Crystallisation from hexane afforded the pure *title compound*, m.p. 203°, $[\alpha]_D^{21}$ + 132° (*c* 1.21 $CHCl_3$), λ_{max} (EtOH) 244nm (ε_{max} 29200), ν_{max} ($CHBr_3$) 3540 (OH), 1708 (C=O), 992 (C−O), δ(CDCl$_3$) includes

4.29 (t7:1H), 3.84 (s:3H), 3.29 (d15:1H).

Example 5

23[E]-Hydroxyimino Factor A

Hydrolysis of the product of Example 3 according to the method described in Example 3 above gave a product which was purified by chromatography over Merck Kieselgel 60 230-400 mesh (400ml) eluting with hexane: ethyl acetate (1:1) to afford the *title compound* as a colourless foam $[\alpha]_D^{21}$ + 140° (*c* 1.24, $CHCl_3$), λ_{max} (EtOH) 244nm (ε_{max} 26700) ν_{max} ($CHBr_3$) 3565, 3490 (OH), 1710 (C=0), 994 (C−0), δ($CDCl_3$) include 8.11 (S:1H), 4.29 (t7:1H), 3.41 (d15:1H).

Example 6

23[E]-Ethoxyimino Factor A

A solution of anhydrous sodium acetate (140mg) in water (3 ml) was added to a solution of 23-keto Factor A (200mg, Example 23 in UK Patent Specification 2176182) and ethoxyamine hydrochloride (126 mg) in methanol (20ml). After 2h at 20° the solution was diluted with ether (40ml) and washed with water. The dried organic phase was evaporated and the resultant off white foam was purified by chromatography over Merck Kieselgel 60 230-400 mesh (90ml). Elution of the column with hexane: ethyl acetate (2:1) afforded the *title compound* as a colourless foam (189mg) $[\alpha]_D^{21}$ + 125° (*c* 1.00, $CHCl_3$) λ_{max} (EtOH) 244mm (ε_{max} 28,200) ν_{max} ($CHBr_3$) 3540, 3480 (OH), 1705 (C=0), 990 (C−0), δ($CDCl_3$) include 4.30 (t7:1H), 4.10 (q7:2H), 3.31 (d15:1H), 1.24 (t7:3H).

The compounds of Examples 7, 8 and 9 were prepared in a similar manner from 23-keto Factor A and the appropriate alkoxyamine.

Example 7

23[E]-Allyloxyimino Factor A

$[\alpha]_D^{21}$ + 124° (*c* 1.17, $CHCl_3$), λ_{max} (EtOH) 244mm (ε_{max} 28,400), ν_{max} ($CHBr_3$) 3550, 3490 (OH), 1708 (C=0), 990 (C−0), δ($CDCl_3$) include 5.98 (m;1H), 5.28 (dd17,2;1H), 5.15 (dd9,2;1H), 4.5-4.7 (m;2H), 4.29 (t7;1H), 3.36 (d14;1H) was prepared from allyloxyamine hydrochloride.

Example 8

23[E]-Isopropyloxyimino Factor A

$[\alpha]_D^{21}$ + 116° (*c* 0.97, $CHCl^3$), λ_{max} (EtOH) 244mm (ε_{max} 25,000), ν_{max} $CHBr_3$) 3550, 3490 (OH), 1708 (C=0), 992 (C−0), δ($CDCl_3$) include 4.2-4.4 (m;2H), 3.30 (d14;1H), 1.21 (d7;3H), 1.20 (d7;3H) was prepared from isopropyloxyamine hydrochloride.

Example 9

23[E]-n-Butoxyimino Factor A

$[\alpha]_D^{21}$ + 115° (*c* 1.10, $CHCl_3$), λ_{max} (EtOH) 244nm (ε_{max} 31,800), ν_{max} ($CHBr_3$) 3540, 3460 (OH), 1708 (C=0), 992 (C−0), δ ($CDCl_3$) include 4.28 (t6;1H), 4.03 (m;2H), 3.96 (d6;1H), 3.31 (d14;1H), 0.9-1.1 (m;15H) was prepared from n-butoxyamine hydrochloride.

Example 10

23[E]-Methoxyimino Factor A,5-acetate

(1) A 3-molar solution of methylmagnesium iodide in ether (0.16ml) was added to a stirred solution of the product of Example 3 (120mg) in dry hexamethylphosphoric triamide (5ml) under nitrogen. Iodomethane (0.09ml) was added, and after 1h, the mixture was diluted with ethyl acetate (30ml) and washed successively with 2N hydrochloric acid and water. The dried organic phase was evaporated and the yellow gum was purified by chromatography over Merck Kieselgel 60 230-400mesh (80ml). Elution of the column with hexane:ethyl acetate (2:1) afforded the *title compound* as a white foam $[\alpha]_D^{21}$ + 123° (c 1.25, $CHCl_3$) λ_{max} (EtOH) 245nm (ε_{max} 30,300). NMR was as described above in Example 2.

(ii) The product of Example 3 (0.082g) was dissolved in diethyl ether (10ml) containing silver oxide (0.4g), freshly prepared form aqueous silver nitrate and 2M sodium hydroxide). The mixture was stirred at room temperature for 2h, whereupon it was filtered and the solvent evaporated to yield a crude yellow gum. This residue was purified by preparative thin layer chromatography (Merck 5717) eluting with dichloromethane/acetone (25:1). The main band was extracted with acetone and evaporated to yield the *title compound* (0.059g) NMR was described above in Exampl 2.

Example 11

23[E]-Methoxyimino Factor A,5-methylcarbamate

Methyl isocyanate (0.13ml, 125mg) and triethylamine (2 drops) were added to a solution of 23[E]-methoxyimino Factor A (350mg) in dry dimethylformamide (0.75ml). The flask was stoppered and heated for 5.5h at 80° with stirring. The reaction mixture was poured into water

(50ml) and the resulting mixture was filtered through kieselguhr. The filter cake was washed with water (150ml) and then extracted with dichloromethane (75ml). The extract was dried ($MgSO_4$) and concentrated to give a yellow foam which was purified by medium pressure column chromatography on silica (125g, Merck Kieselgel 60, 230-400 mesh). Elution with hexane : ethyl acetate (1:1) gave the *title compound* as a white foam (206mg). $[\alpha]_D^{22}$ + 99° (*c* 0.55, CH_2Cl_2); λ_{max} (EtOH) 244.4 nm (ε 28710); ν_{max} ($CHBr_3$) 3530 (OH), 3455 (NH), 1720 (ester), 1720 + 1510 (carbamate) and 993 cm^{-1} (C—O); δ ($CDCl_3$) includes 1.78 (s, 3H), 2.86 (d, 5Hz, 3H), 3.29 (d, 14 Hz, 1H), 3.83 (s, 3H), 4.80 (q, 5 Hz, 1H) and 5.50 (m, 2H).

Example 12

23[E]-Methoxyimino Factor A,5-methylcarbonate

To a solution of 23[E]-methoxyimino Factor A (150mg) in dichloromethane (15ml) and pyridine (0.3ml) stirring at 0° was added methylchloroformate (0.7ml of 1.0M solution in dichloromethane). The reaction mixture was left stirring at 0-3° for 20min., then was added to dichloromethane (70ml) and washed with 2N hydrochloric acid (50ml) and water (50ml). The organic phase was dried ($MgSO_4$) and solvent removed to give a foam which was purified by medium pressure column chromatography on silica (40g, Merck kieselgel 60, 230-400 mesh). Elution with dichloromethane : ethyl acetate (30:1) gave the *title compound* as a white foam (127mg). $[\alpha]_D^{21}$ + 145° (c=0.41, CH_2Cl_2); λ_{max} (EtOH) 244.4 nm (ε 31210); ν_{max} ($CHBr_3$) 3460 + 3540 (OH), 1742 (carbonate) 1710 (ester) and 992 cm^{-1} (C—O); δ ($CDCl_3$) includes 1.82 (s, 3H), 3.29 (d 14 Hz, 1H), 3.82 (s, 3H), 3,83 (s, 3H), 5.2-5.4 (m; 3H) 5.56 (s, 1H).

Example 13

23[E]-Methoxyimino Factor D,5-acetate

A solution containing 23-keto Factor D,5-acetate (251mg, Example 119 in UK Patent Specification 2176182), sodium acetate (250mg) and methoxyamine hydrochloride (250mg) in methanol (40ml) was kept at 20° for 24h, concentrated to *ca* 10ml, diluted with ethyl acetate (50ml), and washed successively with 0.5N hydrochloric acid and water. The dried organic phase was evaporated to afford a yellow foam which was purified by chromatography over Merck Keiselgel 60, 230-400 mesh (120ml). Elution of the column with hexane afford the *title compound* as a pale yellow foam (144 mg); λ_{max} (EtOH) 244nm (ε 26,400), ν_{max} ($CHBr_3$) (cm^{-1}) 3500 (OH), 1732 (OAc), 1710 (C=0); δ ($CDCl_3$) include 5.54 (m; 2H), 4.92 (m; 1H), 3.84 (s; 3H), 3.32 (m; 1H), 3.30 (d14; 1H), 2.17 (s; 3H), 1.91 (d14; 1H) 1.76 (s; 3H), 1.63 (s; 3H), 1.51 (s; 3H), 1.01 (t7,; 3H), 0.99 (d6; 3H), 0.92 (d6; 3H).

Example 14

23[E]-Methoxyimino Factor D

A solution containing the product of Example 13 (140mg) and 1N sodium hydroxide (0.6ml) in methanol (8ml) was stirred in an ice bath for 1.5h. The solution was diluted with ethyl acetate (30ml) and washed successively with 1N hydrochloride acid and water. The dried organic phase was evaporated to afford a yellow foam which was purified by chromatography over Merck Keiselgel 60, 230-400 mesh (50ml). Elution of the column with hexane:ethyl acetate (2:1) afforded the *title compound* as an off-white foam (105mg); $[\alpha]_D^{21}$ + 96° (*c* 1.38, $CHCl_3$); λ_{max} (EtOH) 244nm (ε 26,700); ν_{max} ($CHBr_3$) (cm^{-1}) 3550, 3500 (OH), 1710 (C=0); δ ($CDCl_3$) include 4.93 (m; 1H), 4.30 (t6; 1H), 3.95 (d6; 1H), 3.84 (s; 3H), 3.30 (d14; 1H), 3.27 (m; 1H), 1.88 (s; 3H), 1.64 (s; 3H), 1.52 (s; 3H), 1.01 (t7; 3H), 1.00 (d6; 3H), 0.92 (d6; 3H).

Example 15

23[E]-Methoxyimino Factor B

A solution containing 23-keto Factor B (1g, Example 19 in UK Patent Specification 2176182), sodium acetate (400mg) and methoxyamine hydrochloride (400mg) was stirred at 20° for 20h, concentrated to *ca* 10ml diluted with ethyl acetate, and washed with water. The organic phase was washed successively with 0.5N hydrochloric acid and water, and the dried organic phase was evaporated and the crude product was purified by chromatography over Merck Keiselgel 60, 230-400 mesh (200ml). Elution of the column with ethyl acetate:dichloromethane (1:9) afforded the *title compound* as a white foam (500mg); $[\alpha]_D^{21}$ + 128° (*c* 1.09, $CHCl_3$); λ_{max} (EtOH) 244nm (ε 30,100); ν_{max} ($CHBr_3$) (cm^{-1}) 3540, 3460 (OH), 1708 (c=0); δ ($CDCl_3$) include 5.46 (q6; 1H), 4.03 (d5; 1H), 3.97 (d5; 1H), 3.83 (s; 3H), 3.50 (s; 3H), 3.32 (m; 1H), 3.29 (d14; 1H), 1.82 (s; 3H), 1.68 (d6; 3H), 1.00 (d6; 3H), 0.92 (d6; 3H).

Example 16

23[E]-Methoxyimino Factor C

Anhydrous sodium acetate (0.54g) and methoxyamine hydrochloride (0.58g) were added to a solution of 23-keto Factor C (1.97g, Example 12 in UK Patent Specification 2176182) in methanol (30ml) containing water (5ml) and the mixture was stirred for 30 min at room temperature

ture. Ethyl acetate (30ml) and 0.5M hydrochloric acid (30ml) were added and the aqueous layer re-extracted with ethyl acetate (15ml). The combined organic layers were washed in turn with 0.5M hydrochloric acid, 5% saturated aq. sodium bicarbonate and 10% saturated aq. sodium chloride, then concentrated *in vacuo* to a yellow foam which was purified by chromatography on Merck 9385 silica gel initially developing the column with dichloromethane and then eluting with dichloromethane containing a small amount of ethyl acetate (up to 10%) to give the *title compound* (1.0g); $[\alpha]_D^{21}$ + 64° (*C*1.0, CH_3OH); ^1H NMR ($CDCl_3$) includes the following signals : δ4.95 (m, 1H); 4.29 (t, 1H, 7Hz); 3.96 (d, 1H, 7Hz); 3.85 (s, 3H [= $NOCH_3$]); 3.66 (d, 1H, 10Hz); 1.51 (s, 3H); 1.42 (t, 1H, 12Hz); IR ($CHBr_3$) 3620-3340cm^{-1} (-OH), 1711 cm^{-1}(C=O).

The following are examples of formulations according to the invention. The term 'Active Ingredient' as used hereinafter means a compound of the invention and may be for example the compound of Example 4.

Multidose parenteral injection

Example 1

	% w/v	Range
Active ingredient	2.0	0.1 - 6.0% w/v
Benzyl alcohol	1.0	
Polysorbate 80	10.0	
Glycerol formal	50.0	
Water for Injections	to 100.0	

Dissolve the active ingredient in the polysorbate 80 and glycerol formal. Add the benzyl alcohol and make up to volume with Water for Injections. Sterilize the product by conventional methods, for example sterile filtration or by heating in an autoclave and package aseptically.

Example 2

	% w/v	Range
Active ingredient	4.0	0.1 - 7.5% w/v
Benzyl alcohol	2.0	
Glyceryl triacetate	30.0	
Propylene glycol	to 100.0	

Dissolve the active ingredient in the benzyl alcohol and glyceryl triacetate. Add the propylene glycol and make up to volume. Sterilize the product by conventional pharmaceutical methods, for example sterile filtration, and package aseptically.

Example 3

	%	Range
Active ingredient	2.0 w/v	0.1 - 7.5% w/v
Ethanol	36.0 v/v	
Non-ionic surfactant (e.g. Synperonic PE L44*)	10.0 w/v	
Propylene glycol	to 100.0	

Dissolve the active ingredient in the ethanol and surfactant and make up to volume. Sterilize the product by conventional pharmaceutical methods, for example sterile filtration, and package aseptically.

*Trademark of ICI

Example 4

	%	Range
Active Ingredient	2.0 w/v	0.1 - 3.0% w/v
Non-ionic surfactant (e.g. Synperonic PE F68*)	2.0 w/v	
Benzyl alcohol	1.0 w/v	
Miglyol 840 **	16.0 v/v	
Water for Injections	to 100.0	

Dissolve the active ingredient in the Miglyol 840. Dissolve the non-ionic surfactant and benzyl alcohol in most of the water. Prepare the emulsion by adding the oily solution to the aqueous solution while homogenising using conventional means. Make up to volume. Aseptically prepare and package aseptically.

*Trademark of ICI

** Trademark of Dynamit Nobel

Aerosol spray

	% w/w	Range
Active Ingredient	0.1	0.01 - 2.0% w/w
Trichloroethane	29.9	
Trichlorofluoromethane	35.0	
Dichlorodifluoromethane	35.0	

Mix the Active Ingredient with trichloroethane and fill into the aerosol container. Purge the headspace with the gaseous propellant and crimp the valve into position. Fill the required weight of liquid propellant under pressure through the valve. Fit with actuators and dust-caps.

Tablet

Method of manufacture - wet granulation

	mg
Active Ingredient	250.0
Magnesium stearate	4.5
Maize starch	22.5
Sodium starch glycolate	9.0
Sodium lauryl sulphate	4.5

Microcrystalline cellulose to tablet core weight of 450mg Add sufficient quantity of a 10% starch paste to the active ingredient to produce a suitable wet mass for granulation. Prepare the granules and dry using a tray or fluid-bed drier. Sift through a sieve, add the remaining ingredients and compress into tablets.

If required, film coat the tablet cores using hydroxypropylmethyl cellulose or other similar film-forming material using either an aqueous or non-aqueous solvent system. A plasticizer and suitable colour may be included in the film-coating solution.

Veterinary tablet for small/domestic animal use

Method of manufacture - dry granulation

	mg
Active Ingredient	50.0
Magnesium stearate	7.5
Microcrystalline cellulose to tablet core weight of	75.0

Blend the active ingredient with the magnesium stearate and microcrystailise cellulose. Compact the blend into slugs. Break down the slugs by passing through a rotary granulator to produce free-flowing granules. Compress into tablets.

The tablet cores can then be film-coated, if desired, as described above.

Veterinary intrammary injection

		mg/dose	Range
Active Ingredient		150mg	0.05 - 1.0g
Polysorbate 60	3.0% w/w)	)	
White Beeswax	6.0% w/w)	to 3g)	to 3 or 15g
Arachis oil	91.0% w/w)	)	

Heat the arachis oil, white beeswax and polysorbate 60 to 160°C with stirring. Maintain at 160°C for two hours and then cool to room temperature with stirring. Aseptically add the active ingredient to the vehicle and disperse using a high speed mixer. Refine by passing through a colloid mill. Aseptically fill the product into sterile plastic syringes.

Veterinary slow-release bolus

	% w/w	Range
Active Ingredient		0.25-2g
Colloidal silicon dioxide	2.0)	to required fill weight
Microcrystalline cellulose	to 100.0)	

Blend the active ingredient with the colloidal silicon dioxide and microcrystalline cellulose by using a suitable aliquot blending technique to achieve a satisfactory distribution of active ingredient throughout the carrier. Incorporate into the slow release device and give (1) a constant release of active ingredient or (2) a pulsed release of active ingredient.

Veterinary oral drench

	% w/v	Range
Active Ingredient	0.35	0.01 - 2% w/v
Polysorbate 85	5.0	
Benzyl alcohol	3.0	
Propylene glycol	30.0	
Phosphate buffer	as pH 6.0 - 6.5	
Water	to 100.0	

Dissolve the active ingredient in the Polysorbate 85, benzyl alcohol and the propylene glycol. Add a proportion of the water and adjust the pH to 6.0—6.5 with phosphate buffer, if necessary. Make up to final volume with the water. Fill the product into the drench container.

Veterinary oral paste

	% w/w	Range
Active Ingredient	4.0	1 - 20% w/w
Saccharin sodium	2.5	
Polysorbate 85	3.0	
Aluminium distearate	5.0	
Fractionated coconut oil	to 100.0	

Disperse the aluminium distearate in the fractionated coconut oil and polysorbate 85 by heating. Cool to room temperature and disperse the saccharin sodium in the oily vehicle. Disperse the active ingredient in the base. Fill into plastic syringes.

Granules for veterinary in-feed administration

	% w/w	Range
Active Ingredient	2.5	0.05-5% w/w
Calcium sulphate, hemi-hydrate	to 100.0	

Blend the Active Ingredient with the calcium sulphate. Prepare the granules using a wet granulation process. Dry using a tray or fluid-bed drier. Fill into the appropriate container.

Veterinary Pour-on

	% w/v	Range
Active Ingredient	2.0	0.1 to 30%
Dimethyl sulphoxide	10.0	
Methyl Isobutyl ketone	30.0	
Propylene glycol (and pigment)	to 100.0	

Dissolve the active ingredient in the dimethyl sulphoxide and the methyl isobutyl ketone. Add the pigment and make up to volume with the propylene glycol. Fill into the pour-on container.

Emulsifiable Concentrate

Active ingredient	50g
Anionic emulsifier (e.g. Phenyl sulphonate CALX)	40g
Non-ionic emulsifier (e.g. Synperonic NP13) *	60g

Aromatic solvent (e.g. Solvesso 100) to 1 litre. Mix all ingredients, stir until dissolved. * Trademark of ICI

Granules

(a)	Active ingredient	50g
	Wood resin	40g
	Gypsum granules (20-60 mesh) (e.g. Agsorb 100A)	to 1kg
(b)	Active ingredient	50g
	Synperonic NP13 *	40g
	Gypsum granules (20-60 mesh)	to 1kg.

Dissolve all ingredients in a volatile solvent e.g. methylene chloride, add to granules tumbling in mixer. Dry to remove solvent.

* Trademark of ICI

The pesticidal activity of the compounds of the invention was determined using a variety of pests and their hosts according to the following general procedure:

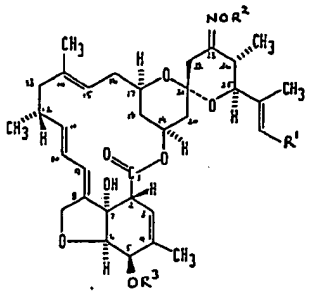
The product was used in the form of a liquid preparation. The preparations were made by dissolving the product in acetone. The solutions were then diluted with water containing 0.1% or 0.01% by weight of a wetting agent until the liquid preparations contained the required concentration of the product.

The test procedure adopted with regard to most pests comprised supporting a number of the pests on a medium which was usually a host plant and either treating the medium with the preparation (residual test) or in the case of *Tetranychus urticae, Myzus persicae, Nilaparvata lugens* and *Musca domestica*, both the pests and the medium were treated with the preparation (contact test). In the case of *Meloidogyne incognita* the solution was applied to soil in which tomato plants were growing, subsequently treated with nematodes and the reduction in the number of root-knots assessed in comparison with a control plant.

Following these procedures, the compound of formula (I) in which R^1 is isopropyl, R^2 is methyl and R^3 is hydrogen was found to be effective at concentrations (by weight of product) of 100 parts per million or less.

CLAIMS

1. Compounds of formula (I)



(I)

and salts thereof, wherein
R^1 represents a methyl, ethyl or isopropyl group;
R^2 represents a hydrogen atom, a C_{1-8} alkyl group or a C_{3-8} alkenyl group and the group $=NOR^2$ is in the E-configuration;
OR^3 is a hydroxyl group or a substituted hydroxyl group having up to 25 carbon atoms.

2. Compounds according to claim 1 in which OR^3 is a methoxycarbonyloxy, acetoxy, methoxy or hydroxyl group.

3. Compounds according to claim 1 in which OR^3 is a hydroxyl group.

4. Compounds according to any preceding claim in which R^1 is an isopropyl group.

5. Compounds according to any preceding claims in which R^2 is a methyl group.

6. Compounds according to claim 1 in which R^1 is an isopropyl group, R^2 is a methyl group and OR^3 is a hydroxy, acetoxy or methoxycarbonyloxy group.

7. The compound according to claim 1 in which R^1 is an isopropyl group, R^2 is a methyl group and OR^3 is a hydroxyl group.

8. The compounds according to claim 1 in which R^1 is a methyl group, R^2 is a methyl group and OR^3 is a methoxy group; or R^1 is an ethyl group, R^2 is a methyl group and OR^3 is a hydroxyl group.

9. A composition for use in human medicine containing an effective amount of at least one compound according to claim 1 together with one or more carriers and/or excipients.

10. A composition for use in veterinary medicine containing an effective amount of at least one compound according to claim 1 together with one or more carriers and/or excipients.

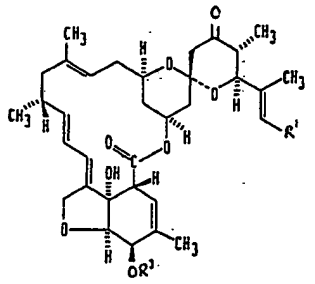
11. A pest control composition containing an effective amount of at least one compound according to claim 1 together with one or more carriers and/or excipients.

12. A composition as claimed in any of claims 9 to 11 containing an effective amount of the compound according to claim 7 together with one or more carriers and/or excipients.

13. A method for combatting pests in agriculture, horticulture or forestry, or in stores, buildings or other public places or locations of the pests, which comprises applying to plants or other vegetation or to the pests themselves or a location thereof an effective amount of one or more compounds according to claim 1.

14. A method as claimed in claim 13 in which said pests are insect, acarine or nematode pests.

15. A process for the preparation of a compound according to claim 1 which comprises:
(A) reacting a compound of formula (II)



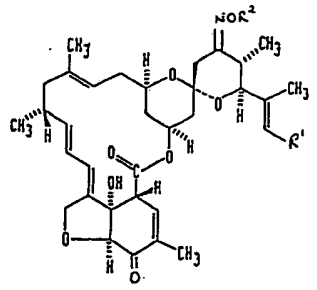
(II)

with a reagent H_2NOR^2 or a salt thereof (R^1, R^2 and OR^3 being as defined in claim 1), if desired followed by deprotection of a compound of formula (I) produced in which OR^3 is a protected hydroxyl group;
(B) in the preparation of a compound of formula (I) in which R^2 is a C_{1-8} alkyl or C_{3-8} alkenyl group and OR^3 is a substituted hydroxyl group, reacting a corresponding compound of formula (I) in which OR^3 is a hydroxyl group with a reagent for converting a hydroxyl group into a

substituted hydroxyl group;

(C) in the preparation of a compound of formula (I) in which R^2 is a C_{1-8} alkyl or C_{3-8} alkenyl group, reacting a compound of formula (I) in which R^2 is a hydrogen atom and OR^3 is a substituted hydroxyl group with an etherifying agent R^2Y (where R^2 is a C_{1-8} alkyl or C_{3-8} alkenyl group and Y is a leaving group), and if desired followed by deprotection of a compound of formula (I) in which OR^3 is a protected hydroxyl group;

(D) in the preparation of a compound of formula (I) in which OR^3 is a hydroxyl group, reducing a compound of formula (III)



(III)

(E) in the preparation of a compound of formula (I) in which OR^3 is a hydroxyl group, deprotecting a corresponding compound of formula (I) in which OR^3 is a protected hydroxyl group; or

(F) in the preparation of a salt of an acid of formula (I), treating said acid with a base or converting one salt into another by exchange of ion.

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